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| 10/633,629 | 08/05/2003 | Ayoub Rashtchian | 38266-0009 | 6375 |

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| EXAMINER | |
|---|---|
| POPA, ILEANA | |
| **ART UNIT** | **PAPER NUMBER** |
| 1633 | |

DATE MAILED: 04/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/633,629 | RASHTCHIAN ET AL. | |
| | Examiner | Art Unit | |
| | Ileana Popa | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *5,6,19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-18 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicant's election without traverse of the species of fluorescent nucleic acid-binding dye, 1520-US, and O-30, in the reply filed on 02/24/2006 is acknowledged.

Claims 5, 6,19, and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 1-4, 7-18, and 21 are pending.

### *Double Patenting*

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claim 1 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 17 of copending Application No. 10/766,312. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claim is drawn to a method of detecting a target nucleic acid in a sample comprising amplifying the target nucleic acid using a polymerase chain reaction, wherein the polymerase chain reaction is carried out in the presence of an effective amount of at least one anti-foam reagent that does not substantially inhibit the action of the polymerase. The application claims are drawn to a method of amplifying a nucleic acid molecule comprising incubating an RNA template with a composition comprising a buffer, two or more reverse transcriptases, and at least on DNA polymerase under conditions that relieve reverse transcriptase-mediated inhibition of DNA polymerase activity and that are sufficient to amplify a DNA molecule complementary to all or a portion of said RNA template (claim 1); and the buffer comprises an effective amount of an anti-foam compound, i.e., an anti-foam compound that does not substantially inhibit the action of the polymerase (claim 17). The instant claims do not recite RT-PCR or a composition comprising two or more reverse transcriptases. However, the specification discloses that the detection of the target nucleic acid could be by RT-PCR and a variety of reverse transcriptases could be used (p. 2, paragraph 0014, p. 4, paragraph 0037). Moreover, the instant claim 1 recites a method of detecting a nucleic acid "comprising

the step of amplifying the target nucleic acid" by PCR; "comprising" is an open term and does not limit the number of reverse transcriptases to be used by the method. Additionally, the open term " comprises" includes the limitation of the RT-PCR taking place "under conditions that relieve reverse transcriptase-mediated inhibition of DNA polymerase activity and that are sufficient to amplify a DNA molecule complementary to all or a portion of said RNA template".

Thus, the co-pending application claims 1 and 17 anticipate the instant claim 1. Since the US Application No. 10/766,312 claims 1 and 17 embrace all limitation of the instant claim, the instant claim and the application claims are obvious variants of one another.

***Claim Rejections - 35 USC § 102***

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-4, 11 and 15-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Li et al. (Brain Research Protocols, 2000, 5: 211-217), as evidenced by www.dermaxime.com/alcohol.htm.

Li et al. teach quantification of mRNA expression by TaqMan real-time RT-PCR, which is carried out in a MicroAmp Optical 96-well reaction plate, wherein each well contains the master mix (Abstract, p. 213, column 1 bridging column 2), i.e., the reaction takes place in a device with a plurality of sample chambers containing the reagents necessary for detecting the target nucleic acids; amplification of the target nucleic acid is performed using a thermostable AmpliTaq Gold DNA polymerase (p. 213, column 1 bridging column 2) and detection is optical detection (p. 213, Fig. 1). Li et al. also teach that the method can be a high throughput method (p. 216, column 1, third paragraph), i.e., can be used to detect different target nucleic acids. Li et al teach that the reaction is performed in a master mix comprising Tween 20 and glycerol (p. 212, column 1, Supply and reagents). Alcohols are known to be antifoaming agents (see www.dermaxime.com/alcohol.htm) and since glycerol is an alcohol, absent evidence to the contrary the reaction is performed in the presence of an anti-foaming agent that does not inhibit polymerase activity. Since Li et al. teach **(i)** a method of detecting a target nucleic acid in a sample by quantitative RT-PCR in the presence of at least one anti-foaming agent that does not inhibit polymerase activity, wherein the detection is optical detection and the reaction takes place in a plurality of sample chambers containing the reagents suitable for the detection of one or more target nucleic acids, and **(ii)** a composition for amplifying a target nucleic acid comprising at least one primer molecule that hybridizes to the target nucleic acid, nucleotide triphosphates, a thermostable DNA polymerase, a detergent, and an effective amount of at least one

anti-foam reagent that does not substantially inhibit the action of the thermostable DNA polymerase, the claimed invention is anticipated by the above-cited art.

Claims 1, 8, 11, and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Stemmer et al. (US Patent No. 5,834,252).

Stemmer et al. teach PCR using a thermostable DNA polymerase (column 3, lines 29-26). Stemmer et al. teach that the PCR buffers could comprise detergent and anti-foaming agents, i.e., the reaction buffer could comprise more than one anti-foaming agent that do not inhibit polymerase activity (column 10, lines 7-30). Since Stemmer et al. teach **(i)** a method of detecting a target nucleic acid in a sample by PCR in the presence of at least two anti-foaming agents that do not inhibit polymerase activity, and **(ii)** a composition for amplifying a target nucleic acid comprising at least one primer molecule that hybridizes to the target nucleic acid, nucleotide triphosphates, a thermostable DNA polymerase, a detergent, and an effective amount of at least two anti-foam reagents that do not substantially inhibit the action of the thermostable DNA polymerase, the claimed invention is anticipated by the above-cited art.

6. Claims 1-4, 11, and 15-18 are rejected under 35 U.S.C. 102(e) as being anticipated by Heid et al. (US Patent No. 6,358,679), as evidenced by www.dermaxime.com/alcohol.htm.

Heid et al. teach a method of amplifying and detecting a target nucleic acid in a sample by real- time RT-PCR, i.e., using a reverse transcriptase in the RT step (column

2, lines 45-63, column 6, lines 10-15 and 64-67) and a thermostable DNA polymerase (AmpliTaq Gold) in the second step, for the amplification of the target nucleic acids (column 18, Example 2). Heid et al. teach estimation of amplified target nucleic acid by optical detection (column 3, lines 3-7, column 8, lines 37-42, column 11lines 17-63). Reaction can be a high throughput reaction (i.e., different nucleic acid targets can be detected) that is carried out in microtiter, microwell format, i.e., the reaction is carried out in a device comprising a plurality of sample chambers, which microwells contain the reagents necessary for the detection of the target nucleic acid (column 7, lines 8-20, column 14 bridging column 15). Heid et al. also teach that the reaction is performed in the presence of Tween 20 and glycerol (column 18, Example 2). Alcohols are known to be antifoaming agents (see www.dermaxime.com/alcohol.htm) and since glycerol is an alcohol, absent evidence to the contrary, the reaction is performed in the presence of an anti-foaming agent that does not inhibit polymerase activity. Since Heid et al. teach **(i)** a method of detecting a target nucleic acid in a sample by quantitative RT-PCR in the presence of at least one anti-foaming agent that does not inhibit polymerase activity, wherein the detection is optical detection and the reaction takes place in a plurality of sample chambers containing the reagents suitable for the detection of one or more target nucleic acids, and **(ii)** a composition for amplifying a target nucleic acid comprising at least one primer molecule that hybridizes to the target nucleic acid, nucleotide triphosphates, a thermostable DNA polymerase, a detergent, and an effective amount of at least one anti-foam reagent that does not substantially inhibit the

action of the thermostable DNA polymerase, the claimed invention is anticipated by the above-cited art.

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-4, 7, 11, 15-18, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blaschke et al. (J Immunol Methods, 2000, 246: 79-90), in view of both Stemmer et al. (US Patent No. 5,834,252) and Varadaraj et al. (Gene, 1994, 140: 1-5, Abstract), as evidenced by Swerdlow et al. (Anal Chem, 1997, 69: 848-855, Abstract).

Blaschke et al. teach real-time RT-PCR for the simultaneous detection of multiple cytokines by measuring the fluorescence emitted by SBR Green (i.e., optical detection of different target nucleic acids using a fluorescent nucleic acid-binding dye) using a reverse transcriptase in the RT step and a thermostable Taq polymerase in the amplification step (p. 80, column 2, first paragraph, p. 82, column 1, second paragraph. Reaction takes place in the LightCycler in glass capillaries that contain the reagents for the detection of nucleic acids (i.e., reaction is carried out in a device comprising a plurality of sample chambers, wherein each sample chamber contains the reagents suitable to detect the target nucleic acid) (p. 82, column 1, second paragraph).

Blaschke et al. do not teach using detergents or anti-foaming agents in the reaction buffer. Stemmer et al. teach the use of both detergents and anti-foaming agents in the PCR buffer (column 10, lines 7-30). It would have been obvious to one of skill in the art, at the time the invention was made, to detect target nucleic acids in a sample by modifying the method of Blaschke et al. to include detergents and anti-foaming agents in the reaction buffer, as taught by Stemmer et al. The motivation to include detergent is provided by Varadaraj et al., who teach that addition of detergents such as Tween-20 and NP-40 improves the specificity of the amplified products, especially when one deals with G+C-rich DNAs. Additionally, since it is known in the art that air bubbles interfere with the microfluidic technology (see Swerdlow et al.) and detergents create air bubbles, one would have been motivated to add an anti-foaming agent to eliminate these bubbles. One would have been expected to have a reasonable expectation of success because the art teaches the successful amplification of target nucleic acids by using detergents and anti-foaming agents in the PCR buffer. Thus, the claimed invention was prima facie obvious at the time the invention was made.

Claims 1, 9, 11, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable Stemmer et al., in view of Kyle (US Patent No. 5,658,767).

Stemmer et al. teach PCR using a thermostable DNA polymerase (column 3, lines 29-26). Stemmer et al. teach the use of both detergents and anti-foaming agents in the PCR buffer (column 10, lines 7-30). Stemmer et al. do not specifically teach the use of silicone-based 1520-US as an anti-foaming agent. Kyle et al. teach the 1520-US

as a suitable anti-foaming agent (column 11, Example 3). It would have been obvious to one of skill in the art, at the time the invention was made, to use the method of Stemmer et al. with 1520-US as an anti-foam agent, with a reasonable expectation of success. The motivation to do so is provided by Kyle et al., who teach 1520-US as an effective anti-foaming agent. One would have been expected to have a reasonable expectation of success because the art teaches the use of anti-foaming agents to control production of foam. Thus, the claimed invention was prima facie obvious at the time the invention was made.

Claims 1, 8, 10-12, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable Stemmer et al. taken with Kyle, as applied to claims 1, 9, 11, and 13 above, in further view of the Sigma catalog (1998) and Wierenga (US Patent No. 5,968,889).

Stemmer et al. taken with Kyle do not teach two anti-foaming agents. However, the Sigma catalog teaches that anti-foaming agents can be supplied as a mixture of organic anti-foams and silicone-based anti-foams,and that O-30 is an organic antifoaming agent. It would have been obvious to one of skill in the art, at the time the invention was made, to detect target nucleic acids in a sample according to Stemmer et al. taken with Kyle, and add a second organic anti-foaming agent, such as O-30, with a reasonable expectation of success. The motivation to do so is provided by Wierenga who teaches that silicone-based anti-foaming agents are not that effective, and that the addition of organic anti-foamers results in a synergistic anti-foaming combination

(Abstract, column 1, lines 38-51, and also column bridging column 2). One would have had a reasonable expectation of success in using such a combination because Sigma catalog describes such combinations and because the art teaches that such combinations are very efficient in controlling foam formation. Thus, the claimed invention was prima facie obvious at the time the invention was made.

9. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ileana Popa

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